1600 #7 1646

Attorney Docket No. CGMAR-013/02US

PATENT

I hereby certify that this correspondence is being HAND-CARRIED to the U.S. Patent and Trademark Office in Washington, D.C., on .

By:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Vincent DUBOIS, et al.

Serial No.: 09/879,442 Examiner: Not Yet Assigned

Confirmation No.: Not Yet Assigned Art Unit: Not Yet Assigned

Filed: June 11, 2001

For: ENZYME-CLEAVABLE PRODRUG COMPOUNDS

Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Transmitted herewith, are the following documents:

- [X] Information Disclosure Statement under 37 C.F.R. §1.97(b),
- [X] Form PTO/SB/08
- [X] International Search Report for PCT/US99/30393
- [X] Cited References (123 documents)
- [X] Return post card

In accordance with 37 C.F.R. §1.97(b), no additional fee for submission of the IDS is required.

580803 v1/PA
CG5F011.DOC

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 03-3117.

Dated: November 29, 2001

Respectfully submitted,
COOLEY GODWARD LLP

Cooley Godward LLP
ATTN: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 843-5000
Fax: (650) 857-0663

By: Karen E. Flick

Karen E. Flick
Reg. No. 44,111

KEF/sb

580803 v1/PA
CG5F01!.DOC

IDS/#7 1/17/02

Attorney Docket No.: QUL-015/02US

PATENT

I hereby certify that this correspondence is being HAND-CARRIED to the U.S. Patent and Trademark Office in Washington, D.C., on .

By: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of Vincent DUBOIS, et al.

Serial No.: 09/879,442 Examiner: Not Yet Assigned

Confirmation No.: Not Yet Assigned Art Unit: Not Yet Assigned

Filed: June 11, 2001

For: ENZYME-CLEAVABLE PRODRUG COMPOUNDS

Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97(b)

In accordance with the duty of disclosure set forth in 37 C.F.R. §1.56, Applicant(s) hereby submits the following information in conformance with 37 C.F.R. §§1.97 and 1.98.

[X] Pursuant to 37 C.F.R. §1.98, a copy of each document cited in the attached Form PTO/SB/08 is enclosed.

[X] Publication(s) **F3, F9, F10, F14, F16, D1, D23, D43, D50, D51, D80, D84, D88** and **D93**, listed on the attached Form PTO/SB/08, were cited in a foreign search or examination report corresponding to PCT application serial no. PCT/US99/30393 and mailed on June 28, 2000. The present application is a CIP of PCT/US99/30393

[X] Enclosed is a copy of a non-English publication(s) **F3** and **F8**. Pursuant to §609 of the M.P.E.P., Applicant submits the attached foreign search or examination report, which cites such non-English language publication(s). Publications **F3** and **F8** are provided as B1 publications which contain English language claims.

[X] Enclosed is a copy of a non-English publications **F1, F2, F4, F7** and **F14**. English language publications **P2, P3, P4, P7** and **P13** (copies enclosed) claim priority from or are otherwise equivalent to these non-English publications, respectively. Therefore these English language references have been submitted in addition to the foreign language references and in lieu of translation of the foreign language references.

This Information Disclosure Statement is filed within any one of the following time periods:

[] within three months from the filing date of this national application other than a CPA under 37 C.F.R. § 1.53(d);

[] within three months from the date of entry of the national stage as set forth in 37 C.F.R. §1.491 in this international application;

[X] before the mailing date of a first office action on the merits; or

[] before the mailing of a first office action after the filing of a request for continued examination under 37 C.F.R. § 1.114.

In accordance with 37 C.F.R. §1.97(b), no additional fee for submission of the IDS is required.

It is respectfully requested that the Examiner consider the above-noted information and return an initialed copy of the attached Form PTO/SB/08 to the undersigned.

Dated: November 29, 2001

Respectfully submitted,
COOLEY GODWARD LLP

Cooley Godward LLP
ATTN: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 843-5000
Fax: (650) 857-0663

By: Karen E. Flick

Karen E. Flick
Reg. No. 44,111

KEF/sb

Please type a plus sign (+) inside this box [+]

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.	U.S. Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY
	P1	4,277,466		Trouet et al.	07-07-1981
	P2	4,296,100		Baurain et al.	10-20-1981
	P3	4,376,765		Trouet et al.	03-15-1983
	P4	4,388,305		Trouet et al.	06-14-1983
	P5	4,639,456		Trouet et al.	01-27-1987
	P6	4,671,958		Rodwell et al.	06-09-1987
	P7	4,703,107		Monsigny et al.	10-27-1987
	P8	4,719,312		Firestone, R.A.	01-12-1988
	P9	4,870,162		Trouet et al.	09-26-1989
	P10	5,024,835		Rao et al	06-18-1991
	P11	5,220,001		Ok et al	06-15-1993
	P12	5,599,686		DeFeo-Jones et al.	02-04-1997
	P13	5,962,216		Trouet, et al.	10-05-1999

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Office	Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	T
	F1	BE	869 485	A		12-01-1978	
	F2	BE	882 541	A		07-16-1980	
	F3	EP	0 037 388	B1	INSTITUT INTERNATIONAL DE PATHOLOGIE CELLULAIRE ET MOLECULAIRE	03-30-1981	
	F4	EP	0 041 935	A1	OMNICHEM	12-16-1981	
	F5	EP	0 044 090	A2	MERCK & CO.	01-20-1982	
	F6	EP	0 126 344	A2	ABBOTT LABORATORIES	11-28-1994	
	F7	EP	0 126 685	A1	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE	11-28-1984	
	F8	EP	0 208 615	B1	IRE-CELLTARG	01-14-1987	
	F9	EP	0 475 230	A1	BRUNSWICK CORPORATION	09-02-1991	
	F10	EP	0 640 622	A1	DRUG DELIVERY SYSTEM INSTITUTE, LTD.	02-29-1994	
	F11	WO	92/07068	A1	ATHENA NEUROSCIENCES, et al.	04-30-1992	
	F12	WO	93/02703		IGEN, INC.	02-18-1993	
	F13	WO	96/00503		MERCK & CO., INC.	01-11-1996	
	F14	WO	96/05863	A1	LA REGION WALLONNE, et al.	02-29-1996	
	F15	WO	96/33198	A1	DRUG INNOVATION & DESIGN, INC.	10-24-1996	
	F16	WO	98/52966	A1	THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE	11-26-1998	
	F17	WO	00/33888	A2	COULTER PHARMACEUTICALS, INC., et al	06-15-2000	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Please type a plus sign (+) inside this box → [PE]

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

MOV 3 0 2001

U.S. PATENT AND TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	D1	ABOLD-PIRAK, Esther, et al., "Cytotoxic activity of Daunorubicin or Vindesin Conjugated to a Monoclonal Antibody on Cultured MCF-7 Breast Carcinoma Cells," *Biochem. Pharmacol.* 38:641-648 (1989)	
	D2	BALAJTHY et al., "Synthesis and Functional Evaluation of a Peptide Derivative of 1-ß-D-Arabinofuranosylcytosine," *J. Med. Chem.* 35:3344-3349 (1992)	
	D3	BARRETT, AJ, et al., (eds.) "Thimet oligopeptidase." Handbook of proteolytic enzymes (with cd-rom). [371], 1108-1111. 1998. San Diego, Academic Press.	
	D4	BARRETT, et al., "Thimet Oligopeptidase and Oligopeptidase M or Neurolysin [32]," *Meth. Enzymol.* 248:529-556 (1995)	
	D5	BARRETT, et al., "Chicken liver Pz-peptidase, a thiol-dependent metallo-endopeptidase," *Biochem J* 271:701-706 (1990)	
	D6	BAURAIN et al., "Amino Acid and Dipeptide Derivatives of Daunorubicin. 2. Cellular Pharmacology and Antitumor Activity on L1210 Leukemic Cells in Vitro and in Vivo," *J. Med. Chem* 23:1171-1174 (1980)	
	D7	BAURAIN, et al, "Antitumor Activity of Daunorubicin Linked to Proteins: Lysosomal Hydrolysis and Antitumor Activity of Conjugates Prepared with Peptidic Spacer Arms," *Chemical Abstracts* 97:386 (1982)	
	D8	BAURAIN, et al., "Antitumor Activity of Daunorubicin Linked to Proteins: Lysosomal Hydrolysis and Antitumor Activity of Conjugates Prepared with Peptidic Spacer Arms," Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Vol. 2, 1430-32 (1982)	
	D9	BAURAIN, et al., "Targeting of Daunorubicin by Covalent and Reversible Linkage to Carrier Proteins. Lysosomal Hydrolysis and Antitumoral Activity of Conjugates Prepared with Peptidic Spacers." Drugs Exp. Clin., Vol. 9, pp 303-311, 1983	
	D10	BRICOUT, Herve, et al., "Synthetic and Kinetic Aspects of Nickel-Catalysed Amination of Allylic Alcohol Derivatives," *Tetrahedron* 54:1073-1084 (1998)	
	D11	BUCHLER, M, et al. "Proteinase yscD (oligopeptidase yscD). Structure, function and relationship of the yeast enzyme with mammalian thimet oligopeptidase (metalloendopeptidase, EP 24.15)," *Eur.J.Biochem.* 219:627-639 (1994)	
	D12	CAMARGO, AC, et al. "Structural requirements of bioactive peptides for interaction with endopeptidase 22.19," *Neuropeptides* 26:281-287 (1994)	
	D13	CARDOZO, C, et al. "Evidence that enzymatic conversion of N-[1(R,S)-carboxy-3-phenylpropyl]- Ala-Ala-Phe-p-aminobenzoate, a specific inhibitor of endopeptidase 24.15, to N-[1(R,S)-carboxy-3-phenylpropyl]-Ala-Ala is necessary for inhibition of angiotensin converting enzyme," *Peptides* 14:1259-1262 (1993)	
	D14	CASALE, L, et al. "Quantitation of endopeptidase 24.11 and endopeptidase 24.15 in human blood leukocytes," *Enzyme Protein* 48:143-148 (1994)	
	D15	CHAIRES, et al., "Self-Association of Daunomycin," *Biochemistry* 21:3927-32 (1982)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

580804 v1/PA

Please type a plus sign (+) inside this box

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

NOV 30 2001

PATENT & TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	3	of	7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

	D16	CHAKRAVARTY et al., "Plasmin-Activated Prodrugs for Cancer Chemotherapy. 1. Synthesis and Biological Activity of Peptidylacivicin and Peptidylphenylenediamine," *J. Med. Chem.* 26:633-638 (1983)	
	D17	CHAKRAVARTY et al., "Plasmin-Activated Prodrugs for Cancer Chemotherapy. 2. Synthesis and Biological Activity of Peptidyl Derivatives of Doxorubicin," *J. Med. Chem.* 26:638-644 (1983)	
	D18	CHEN, et al. "Immunolocalization of thimet oligopeptidase in chicken embryonic fibroblasts," *Exp. Cell Res* 216:80-85 (1995)	
	D19	CHEN, et.al., " 'Analogous' Organic Synthesis of Small-Compound Libraries: Validation of Combinatorial Chemistry in Small Molecule Synthesis," *J. Am. Chem. Soc.* 116:2661 (1994)	
	D20	CONFALONIERI, et al., "The use of new laser particle sizer and shape analyser to detect and evaluate gelatinous microparticles suspended in reconstituted anthracycline infusion solutions," *J. Pharmaceut. Biomed. Anal.* 9:1-8 (1991)	
	D21	CRACK, et al., "The association of metalloendopeptidase EC 3.4.24.15 at the extracellular surface of the AtT-20 cell plasma membrane," *Brain Res* 835:113-124 (1999)	
	D22	DANDO, et al., "Human thimet oligopeptidase," *Biochem J* 294:451-457 (1993)	
	D23	DE MARRE, et al., "Evaluation of the hydrolytic and enzymatic stability of macromolecular Mitomycin C Derivatives," *J. Controlled Release* 31:89-97 (1994)	
	D24	DELUCIA, et al., "Efficacy and toxicity of differently charged polycationic protamine-like peptides for heparin anticoagulation reversal," *J. Vasc. Surg.* 18:49-60 (1993)	
	D25	DUBOIS, et al. "Pharmacokinetics and Tissue Distribution of CPI-004, a New Prodrug of Doxorubicin, in Normal and Tumor-Bearing Mice." Abstract #3329, American Association for Cancer Research, Scientific Proceedings, April 1-5, 2000.	
	D26	EISENBRAND et al., "An Approach Towards More Selective Anticancer Agents," Synthesis," Synthesis pp. 1246-1258 (October 1996)	
	D27	EKRAMI, et al., "Carbamylation decreases the cytotoxicity but not the drug-carrier properties of polylysines," *J. Drug Targ.* 2:469-475 (1995)	
	D28	FERRO, et al. "Secretion of a neuropeptide-metabolizing enzyme similar to endopeptidase 22.19 by glioma C6 cells," *Biochem.Biophys.Res.Commun.* 191:275-281. (1993)	
	D29	FERRO, et al., "Secretion of metalloendopeptidase 24.15 (EC 3.4.24.15)," *DNA Cell Biol* 18:781-789 (1999)	
	D30	GARRIDO, et al., "Confocal microscopy reveals thimet oligopeptidase (EC 3.4.24.15) and neurolysin (EC 3.4.24.16) in the classical secretory pathway," *DNA Cell Biol* 18:323-331 (1999)	
	D31	GENET, et al., "A General and Simple Removal of the Allyloxycarbonyl Protecting Group by Palladium-Catalyzed Reactionos Using Nitrogen and Sulfur Nucleophiles," *Synlett* 680-682 (1992)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Please type a plus sign (+) inside this box

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	4	of	7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

	D32	GENET, et al., "Practical Palladium-Mediated Deptrotective Method of Allyloxycarbonyl in Aqueous Media," *Tetrahedron*. Vol. 50, No. 2 497-503 (1994)	
	D33	GLUCKSMAN and ROBERTS, "Strategies for characterizing, cloning, and expressing soluble endopeptidases," *Methods in Neurosciences*, 23: 296-316 (1995)	
	D34	HARNOIS-PONTONI, I. *et al.*, "Hydrosoluble Fluorogenic Substrates for Plasmin" Analytical Biochemistry, **193**, 248-255 (1991)	
	D35	HAYASHI, et al. "Species specificity of thimet oligopeptidase (EC 3.4.24.15)," *Biol.Chem Hoppe-Seyler* 377:283-291 (1996)	
	D36	HOES and FEIJEN "The Application of Drug-Polymer Conjugates in Chemotherapy" in Horizons in Biochemistry and Biophysics Vol. 9: Drug Carrier Systems, pp. 57-109 (1989)	
	D37	ISRAEL, M. *et al.*, "Adriamycin Analogues. Preparation and Biological Evaluation of Some N-(Trifluoroacetyl)-14-O-[(N-acetylamino)acyl] adriamycin Derivatives" J. of Med. Chem., 1986, Vol. **29**, 1273-1276	
	D38	JACCHIERI, et al. " comparative conformational analysis of thimet oligopeptidase (EC 3.4.24.15) substrates," *J.Pept.Res* 51:452-459 (1998)	
	D39	JIRACEK, et al. "Development of highly potent and selective phosphinic peptide inhibitors of zinc endopeptidase 24-15 using combinatorial chemistry." *J. Biol. Chem* 270:21701-21706 (1995)	
	D40	KANDUKURI, S. P., *et al.*, "Vinblastin-23-oyl Amino Acid Derivatives: Chemistry, Physicochemical Data, Toxicity and Antitumor Activities against P388 and L1210 Leukemias" Journal of Medicinal Chemistry, 1985, Vol. **28**, No. 8, 1079-1088	
	D41	KATO, et al., "Cloning, amino acid sequence and tissue distribution of porcine thimet oligopeptidase. A comparison with soluble angiotensin-binding protein," *Eur J Biochem* 221:159-165 (1994)	
	D42	KENNETT et al., "Comparative Histochemical, Biochemical and Immunocytochemical Studies of Cathepsin B in Human Gingiva," *Chem. Abstr.*, 121:79924, 1994	
	D43	KING, et al., "Synthesis and proteolytic cleavage of 3'-*N* -peptidyI-Adriamycin prodrugs," *Struct. Biol.* 137-139 (1988)	
	D44	KNIGHT and BARRETT, "Structure/function relationships in the inhibition of thimet oligopeptidase by carboxyphenylpropyl-peptides," *FEBS Lett* 294: 183-186 (1991)	
	D45	KNIGHT, et al. "Thimet oligopeptidase specificity: evidence of preferential cleavage near the C-terminus and product inhibition from kinetic analysis of peptide hydrolysis," *Biochem.J.* 308:145-150 (1995)	
	D46	KRAUSE, et al., "Characterization and localization of mitochondrial oligopeptidase (MOP) (EC 3.4.24.16) activity in the human cervical adenocarcinoma cell line HeLa," *J Cell Biochem* 66:297-308 (1997)	
	D47	LESSER, et al. "Hydrolysis of N-formylmethionyl chemotactic peptides by endopeptidase 24.11 and endopeptidase 24.15," *Peptides* 17:13-16 (1996).	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

580804 v1/PA

Please type a plus sign (+) inside this box

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 5 of 7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

	D48	LEW, et al. "Evidence for a two-step mechanism of gonadotropin-releasing hormone metabolism by prolyl endopeptidase and metal loendopeptidase EC 3.4.24.15 in ovine hypothalamic extracts," *J. Biol. Chem.* 269:12626-12632 (1994)	
	D49	LEW, et al. "Substrate specificity differences between recombinant rat testes endopeptidase EC 3.4.24.15 and the native brain enzyme," *Biochem Biophys Res Commun* 209:788-795 (1995)	
	D50	MASQUELIER, et al., "Amino Acid and Dipeptide Derivatives of Daunorubicin, 1. Synthesis, Physicochemical Properties, and Lysosomal Digestion," *J. Med. Chem.* 23:1166-1170 (1980)	
	D51	MASQUELIER, et al., "Antitumor Activity of Daunorubicin Linked to Proteins: Biological and Antitumor Properties of Peptidic Derivatives of Daunorubicin Used as Intermediates," Curr.Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Vol. 2, 1428-30 (1982)	
	D52	MASQUELIER, M., et al., "Antitumor Activity of Daunorubicin Linked to Proteins: Biological and Antitumor Properties of Peptidic Derivatives of Daunorubicin Used as Intermediates," Chemical Abstracts 97:386 (1982)	
	D53	MATZANKE, et al., "Evidence for Polynuclear Aggregates of Ferric Daunomycin," *Eur. J. Biochem.* 207:747-55 (1992)	
	D54	MAYER, R., *et al.*, "Peptide Derivatives Specific for a *Plasmodium falciparum* Proteinase Inhibit the Human Erythrocyte Invasion by Merozoites" Journal of Medicinal Chemistry, 1991, Vol. **34**, 3029-3038	
	D55	MCKIE, N, et al. "Rat thimet oligopeptidase: large-scale expression in Escherichia coli and characterization of the recombinant enzyme," *Biochem.J.* 309:203-207 (1995)	
	D56	MENOZZI, et al., "Self-association of doxorubicin and related compounds in aqueous solutions," *J. Pharmaceut. Sci.*, 73:766-770 (1984)	
	D57	MOODY, et al., "Neurotensin is metabolized by endogenous proteases in prostate cancer cell lines," *Peptides* 19:253-258 (1998)	
	D58	MORALES, et al., "PZ-peptidase from Chick Embryos. Purification, Properties, and Action on Collagen Peptides," *J Biol Chem* 252:4855-4860 (1977)	
	D59	NOBLE, et al., "Association of aminopeptidase N and endopeptidase 24.15 inhibitors potentiate behavioral effects mediated by nociceptin/orphanin FO in mice," *FEBS Lett.* 401:227-229 (1997)	
	D60	OLIVEIRA, et al., "Characterization of thiol-, aspartyl-, and thiol-metallo-peptidase activities in madin-darby canine kidney cells," *J Cell Biochem* 76:478-488 (2000)	
	D61	ORLOWSKI, et al. "Substrate-related potent inhibitors of brain metalloendopeptidase." *Biochemistry* 27:597-602 (1988)	
	D62	ORLOWSKI, et al., "Endopeptidase 24.15 from rat testes. Isolation of the enzyme and its specificity toward synthetic and natural peptides, including enkephalin-containing peptides," *Biochem J* 261:951-958 (1989)	
	D63	PIEROTTI, et al., "Endopeptidase-24.15 in rat hypothalamic/pituitary/gonadal axis," *Mol Cell Endocrinol* 76:95-103 (1991)	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Please type a plus sign (+) inside this box

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 6 of 7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

	D64	PINEAU, et al. "Distribution of thimet oligopeptidase (E.C. 3.4.24.15) in human and rat testes," *J. Cell Sci* 112:3455-3462 (1999)	
	D65	POZGAY, et al. "Substrate and Inhibitor Studies of Thermolysin-like Neutral Metallopeptidase from Kidney Membrane Fractions: Comparison with Bacterial Thermolysin," *Biochem.* 25:1292-1299 (1986)	
	D66	POZSGAY, M. *et al.*, "A Method for Designing Peptide Substrates for Proteases: Tripeptidal-p-nitroanilide Substrates for Subtilisin Carlsberg" European Journal of Biochemistry Vol. **95**: 115-119 (1979)	
	D67	RINK, "Solid-Phase Synthesis of Protected Peptide Fragments Using a Trialkoxy-Diphenyl-Methylester Resin," *Tet. Lett.* 28:3787 (1987)	
	D68	RIOLI, et al. "Neuropeptide specificity and inhibition of recombinant isoforms of the endopeptidase 3.4.24.16 family: comparison with the related recombinant endopeptidase 3.4.24.15," *Biochem. Biophys. Res Commun.* 250:5-11 (1998)	
	D69	SAID, et al., "Systemic Treatment: Methotrexate" Clinics in Dermatology 15:781-797 (1997)	
	D70	SEITZ et al., "Synthesis and Chemical Properties of a Series of Doxorubicin Enaminomalonyl-. ß- Alanine Derivatives," *Tetrahedron Lett.*, 3:413-1416 (1995)	
	D71	SERIZAWA, et al., "Characterization of a mitochondrial metallopeptidase reveals neurolysin as a homologue of thimet oligopeptidase," *J Biol Chem* 270:2092-2098 (1995)	
	D72	SHAPIRO, et al., "Mild and Rapid Azide-Mediated, Palladium Catalyzed Cleavage of Allylester Based Protecting Groups," *Tetrahedron* 35:5421-5424 (1994)	
	D73	SHRIMPTON, et al., "Thiol Activation of Endopeptidase EC 3.4.24.15," *J. Biol. Chem.* 272:17395-17399 (1997)	
	D74	TABRIZI-FARD, et al., "Evaluation of the Pharmacokinetic Properties of a Doxorubicin Prodrug in Female ICR(CD1®) Mice Following Intravenous Administration," *Proc. Amer. Assoc. Cancer Res*, 42:324 (2001)	
	D75	TAYLOR & AMIDON (eds.) Peptide-Based Drug Design, Controlling Transport and Metabolism, 1995, 423-445, 449-467 (2 chapters)	
	D76	THOMPSON, et al. "Cloning and functional expression of a metalloendopeptidase from human brain with the ability to cleave a beta-APP substrate peptide," *Biochem Biophys Res Commun* 213: 66-73 (1995)	
	D77	TISLJAR and BARRETT "Thiol-dependent metallo-endopeptidase characteristics of Pz-peptidase in rat and rabbit," *Biochem J* 267: 531-533 (1990)	
	D78	TISLJAR, "Thimet oligopeptidase—a review of a thiol dependent metallo-endopeptidase also known as Pz-peptidase endopeptidase 24.15 and endo-oligopeptidase," *Biol Chem Hoppe Seyler* 374: 91-100 (1993)	
	D79	TRAIL, P.A., *et al.*, "Cure of Xenografted Human Carcinomas by BR96-Doxorubicin Immunoconjugates" Science Vol. **261**, 9 July 1993, 212-215	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Please type a plus sign (+) inside this box

PTO/SB/08A (08-00)

Substitute for form 1449A/PTO

NOV 30 2001

PATENT & TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 7 of 7

Complete if Known	
Application Number	09/879,442
Filing Date	June 11, 2001
First Named Inventor	Vincent DUBOIS
Group Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	COUL-015/02US

	D80	TROUET, et al., "A covalent linkage between daunorubicin and proteins that is stable in serum and reversible by lysosomal hydrolases, as required for a lysosomotropic drug-carrier conjugate: *In Vitro* and *vivo* studies," *Proc. Natl. acad. Sci. USA* 79:626-629 (1982)	
	D81	TROUET, et al, "CPI-004: An Extracellularly Tumor-Activated Prodrug of Doxorubicin." Abstract #3328, American Association for Cancer Research, Scientific Proceedings, April 1-5, 2000.	
	D82	TUGWELL, et al., "Methotrexate in Rheumatoid Arthritis" Ann. Internal Med. 107:358-366 (1987)	
	D83	UKAI, et al. "A novel synthetic inhibitor of endopeptidase-24.15," *J. Enzyme Inhib.* 11:39-49 (1996)	
	D84	UMEMOTO, et al., "Preparation and *In Vitro* Cytotoxicity of a Methotrexate-Anti-MM46 Monoclonal Antibody Conjugate *Via* an Oligopeptide Spacer," *Inatl. J. Cancer* 43:677-684 (1999)	
	D85	VAN DER VIJGH, et al. "Comparative metabolism and pharmacokinetics of doxorubicin and 4'-epidoxorubicin in plasma, heart and tumor of tumor-bearing mice," *Cancer Chemother Pharmacol* 26:9-12 (1990)	
	D86	WAKEFIELD, et al., "Heparin-mediated reductions of the toxic effects of protamine sulfate on rabbit myocardium," *J. Vasc. Surg.* 16:47-53 (1992)	
	D87	WALDMANN, et al., "Synthesis of the Palmitoylated and Prenylated C-Terminal Lipopeptides of the Human R- and N-*Ras* Proteins," *Bioorg. Med. Chem.* 7:749 (1998)	
	D88	WALDMANN, and SEBASTIAN, "Enzymatic Protecting Group Techniques," *Chemical Reviews*, 94:911-937 (1994)	
	D89	WANG, "*p*-Alloxybenzyl Alcohol Resin and *p*-Alkoxybenzyloxycarbonylhydrazide Resin for Solid Phase Synthesis of Protected Peptide Fragments," *J. Am. Chem. Soc.* 95:1328 (1973)	
	D90	WHALLEY, "Receptors Mediating the Increase in Vascular Permeability to Kinins: Comparative Studies in Rat, Guinea Pig and Rabbit," Chem. Abstr., #107: 127965, 1987	
	D91	WOLFSON, AJ, et al. Differential activation of endopeptidase EC 3.4.24.15 toward natural and synthetic substrates by metal ions. Biochem.Biophys.Res. Commun. 229[1], 341-348. 12-4-1996.	
	D92	ZHANG, et al. " A Combinatorial Method for the Solid Phase Synthesis of α-Amino Phosphonates and Phosphonic Acids," *Tet. Lett.* 37:5457(1996)	
	D93	MASQUELIER, et al., " Incorporation and Binding of Anthracycline Derivatives to Low Density Lipoprotein: *In vitro* and *in vivo* Studies of Drug-LDL Conjugates," Recent Adv. Chemother., Proc. Int. Congr. Chemother., 14th Volume, Anticancer Section 1, pp. 311-12 (1985)	

[1] Unique citation designation number.
[2] Applicant is to place a check mark here if English language Translation attached.

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

580804 v1/PA